AF/1623

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

In re Patent Application of

von BORSTEL et al

Serial No.: 08/460,186

Filed: June 2, 1996

Atty. Dkt.: 1331-138
C# M#

Group Art Unit: 1623

Examiner: Owens, H.

Date: September 25, 2001

Title: TREATMENT OF CHEMOTHERAPEUTIC AGENT AND ANTIVIRAL AGENT TOXICITY WITH ACYLATED PYRIMIDINE NUCLEOSIDES

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

☐ **NOTICE OF APPEAL**
Applicant hereby appeals to the Board of Appeals from the decision dated _____ of the Examiner twice/finally rejecting claims _____ ($ 310.00) $

☐ An appeal **BRIEF** is attached in triplicate in the pending appeal of the above-identified application ($ 310.00) $ 0.00

☐ An **ORAL HEARING** is requested under Rule 194 ($270.00) (due within two months after Examiner's Answer) $ 0.00

☐ Credit for fees paid in prior appeal without decision on merits -$ (0.00)

☒ A reply brief is attached in triplicate under Rule 193(b) **(no fee)**

☐ Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) **($110.00/1 month**; $390.00/2 months; **$890.00/3 months**; $1390.00/4 months) $ 0.00

SUBTOTAL $ 0.00

☐ Applicant claims "Small entity" status, enter ½ of subtotal and subtract -$(0.00)
☐ "Small entity" statement attached.

SUBTOTAL $ 0.00

Less month extension previously paid on -$(0.00)

TOTAL FEE ENCLOSED $ 0.00

Any future submission requiring an extension of time is hereby stated to include a petition for such time extension. The Commissioner is hereby authorized to charge any deficiency in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Account No. 14-1140.** A duplicate copy of this sheet is attached.

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By Atty.: Leonard C. Mitchard, Reg. No. 29,009

Signature: _____

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Serial No. **08/460,186**
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Atty. Ref.: **1331-138**
Group: **1623**
Examiner: **Owens, H.**

For: **TREATMENT OF CHEMOTHERAPEUTIC AGENT AND ANTIVIRAL AGENT TOXICITY WITH ACYLATED PYRIMIDINE NUCLEOSIDES**

* *

September 25, 2001

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

REPLY BRIEF

Sir:

This is in reply to the Examiner's Answer mailed July 31, 2001.

ISSUES

It is noted, with appreciation, that the 35 USC 112 rejection has been withdrawn. Therefore, the issues now before the Board are:

(1) whether Claims 1-15, 18-19 and 22-25 are unpatentable over Martin et al and Sommadossi et al in view of von Borstel et al (WO 89/03837) and Falcone et al; and

(2) whether Claims 16-17 and 20-21 are unpatentable over Bhalla et al in view of von Borstel and Hanze et al.

The obviousness-type double patenting rejection has been placed in abeyance until allowable subject matter is indicated.

GROUPING OF CLAIMS

The Examiner's Answer indicates that it is in response to the October 13, 2000 Appeal Brief and the May 15, 2001 Supplemental Appeal Brief. The Answer does not mention the Second Supplemental Appeal Brief, dated May 21, 2001, relating to Grouping of the Claims. In view of the withdrawal of the Section 112, first paragraph rejection, noted above, and the argument for separate patentability of claims 20-21 presented below, the Grouping of the Claims should be updated. The new grouping is as follows:

(1) Claims 1-15 and 22-25 stand or fall together on the remaining ground of rejection, alleged obviousness over Martin et al. and Sommadossi et al. in view of von Borstel and Falcone.

(2) Claims 18-19 stand or fall together.

(3) Claims 16-17 stand or fall together.

(4) Claims 20-21 stand or fall together.

SEPARATE PATENTABILITY OF CLAIMS 18-19

Claims 18-19 are directed to a method for preventing or treating toxicity due to a pyrimidine nucleoside analog (e.g. AZT) comprising administering to an

animal an acylated derivative of uridine, deoxyuridine or cytidine; and an inhibitor of uridine phosphorylase. Falcone, et al., Blood (1990) 76(11): 2216-2221 has been cited as a secondary reference teaching the use of an inhibitor of uridine nucleoside phosphorylase, benzylacylouridine (BAU), to increase the serum and tissue levels of free uridine, thereby reducing the toxicity of AZT. Based on Falcone, et al. in combination with the Martin, Sommadossi and von Borstel publications, it allegedly would have been obvious to administer acylated uridine or cytidine in combination with a uridine phosphorylase inhibitor to obtain the combined uridine elevating effects of two compounds known in the art to increase the bioavailability of free uridine.

To make out *a prima facie* case of obviousness, it is not sufficient that the teaching of the prior art could have been modified to arrive at the claimed invention. Rather, the PTO bears the burden of establishing that there was **motivation**, based on the prior art, to do so. As stated by the CAFC in *In re Vaeck*:

> "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should... carry out the process; and (2) whether the prior art would also have revealed that in so... carrying out, those of ordinary skill would have a reasonable expectation of success.... Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, ____ (Fed. Cir. 1991) (internal citations omitted)

In looking for a motivation to combine the references, the Examiner's Answer presents two arguments based on two different allegedly beneficial effects of uridine phorsphorylase inhibitors:

(A) to increase the serum and tissue levels of free uridine; and

(B) to avoid toxicity associated with the degradation of plasma uridine to uracil. Both arguments are wrong.

(a) No Motivation to Further Increase *In Vivo* Uridine

First, in the Examiner's Answer, the PTO has maintained the position that the uridine elevating effects of a uridine phosphorylase inhibitor provide the motivation to combine such an inhibitor with an acylated uridine or cytidine. The Examiner's Answer stated:

> "Applicants [sic] arguments are silent with respect to the motivation provided by Falcone to use an inhibitor of uridine nucleoside phosphorylase as a way to increase serum and tissue levels of free uridine....: a method of using either acylated U or C in combination with a uridine phosphorylase inhibitor would also have been obvious to the person or [sic] ordinary skill in the art at the time of the invention wanting to obtain the combined uridine elevating effects of two compounds known in the art to increase the bioavailability of free uridine." (Examiner's Answer, page 10)

As seen from the above-quoted passage from the Examiner's Answer, the Answer purports to find that the combination of acylated uridine or cytidine and a uridine phosphorylase inhibitor would have been obvious to the person of ordinary skill who wanted to obtain the combined uridine elevating effects of the

two compounds. However, that begs the question of whether those of ordinary skill in the art, seeking to prevent or treat toxicity due to a pyrimidine nucleoside analog (e.g. AZT), would have sought out the combined uridine elevating effects of the combination. They would not, and Falcone, et al. explains why.

The person of ordinary skill in the art would **not** have been motivated to combine an inhibitor of uridine phosphorylase with a source of uridine in order to prevent or treat toxicity due to a pyrimidine nucleoside analog, since Falcone teaches that the increased *in vivo* levels of uridine resulting from such combination did not result in reductions in AZT toxicity as compared to the uridine phosphorylase inhibitor BAU alone or uridine alone. This can be seen from Falcone, et al., which stated:

> "Indeed, our present observation that BAU doses above 300 mg/kg/d, or combinations of BAU with low doses of exogenous Urd, do not result in improved therapeutic efficacy as compared with BAU alone (300 mg/kg/d) supports previous in vitro observations that the maximum ability of exogenous Urd to reverse AZT cytotoxicity is achieved at the relatively low Urd concentration of 50 µmol/L." (Falcone, et al., paragraph bridging pp. 2219-2220)

As seen from the above-quoted passage from Falcone, the person of ordinary skill in the art would **not** have expected that the combination of a uridine phosphorylase inhibitor (such as BAU) and a source of uridine would result in improved efficacy in preventing or treating toxicity due to a pyrimidine nucleoside analog compared to either the uridine phosphorylase inhibitor alone or the source

of uridine alone. Falcone would have led the person of ordinary skill in the art to expect that high plasma levels of uridine, however achieved, are no more effective than relatively lower plasma levels of uridine in counteracting the toxic effects of a pyrimidine nucleoside analog such as AZT. The person of ordinary skill in the art would not have had the reasonable expectation of success necessary to sustain a *prima facie* case of obviousness.

In seeking to counter appellants' argument that Falcone would have led the person of ordinary skill in the art not to have a reasonable expectation of success, the Examiner's Answer wrongly tried to distinguish between nonacylated uridine which allegedly does not increase plasma uridine and acylated uridine which does. The Examiner's Answer stated:

> "The citation by applicant of Falcone in the supplemental brief (paragraph bridging pp. 22 19-20) only shows that exogenous nonacylated uridine does not necessarily increase the beneficial levels of plasma uridine and further supports the examiner s argument for the use of acylated uridine, as taught by Von Borstel, which does increase plasma levels of uridine." (Examiner's Answer, page 9) (underlining in original)

Contrary to the assertion of the Answer, Falcone teaches that higher doses of exogenous nonacylated uridine (Urd) do result in higher plasma levels of uridine in a dose-responsive manner. Falcone states:

> "Analysis of the plasma kinetics of the various Urd doses used in these studies (Fig 3) indicates that for doses below 1,000 mg/kg the clearance

> was rapid (half-life approximately 20 minutes), and the plasma concentration of Urd was normal within 2 to 3 hours. In contrast, at doses above 2,000 mg/kg, plasma Urd levels remained significantly elevated (>1mmol/L) for several hours, probably reflecting a saturation of its clearance." (Falcone, p. 2218, left column; See also Fig. 3)

As seen from the above-quoted passage and from Figure 3 of Falcone, increasing the dose of exogenous nonacylated uridine resulted in increasing plasma levels of uridine *in vivo*. Therefore, the supposed inability of nonacylated uridine to increase plasma levels of uridine is nonexistent and thus cannot be used to explain away Falcone. Falcone taught the person of ordinary skill in the art that increased plasma levels of uridine can be achieved utilizing the combination of uridine and a uridine phosphorylase inhibitor, but that such increased levels did not result in improved efficacy in treating or preventing AZT toxicity.

(b) Falcone Does Not Teach Preventing Uracil Toxicity

Second, in the Examiner's Answer, the PTO has newly taken the position that the ability of a uridine phosphorylase inhibitor to prevent toxicity associated with the degradation of plasma uridine to uracil provides the motivation to combine such an inhibitor with an acylated uridine or cytidine. The Examiner's Answer stated:

> "Falcone teaches that BAU or any uridine phosphorylase inhibitor exerts it's [sic] beneficial effects by preventing the toxic degradation of uridine to uracil. Thus, the combination of two compounds, one that increases the

> plasma levels of uridine (which is beneficial in reducing the toxicity associated with administration of a pyrimidine nucleoside analog such as AZT), and one that prevents the toxicity associated with the degradation of plasma uridine to uracil, such as BAU or any uridine phosphorylase inhibitor, would be obvious to one of skill in the art." (Examiner's Answer, page 9)

Contrary to the assertion in the above-quoted passage from the Examiner's Answer, Falcone nowhere teaches that BAU or any other uridine phosphorylase inhibitor exerts its beneficial effects by preventing the supposedly toxic degradation of uridine to uracil. In fact, Falcone says nothing about uracil toxicity. Rather, Falcone teaches that BAU exerts its beneficial effect by increasing plasma levels of uridine (Urd). Falcone states:

> "In summary, we have demonstrated the therapeutic utility of concomitant BAU and AZT therapy in a murine retroviral model. Enhanced efficacy appears to be related to the ability of BAU to elevate the plasma concentration of Urd and thus reduce AZT-related marrow toxicity, without impeding antiretroviral activity." (Falcone, p. 2220, paragraph bridging left and right columns) (underlining added)

As seen from the above-quoted passage, Falcone taught that the uridine phosphorylase inhibitor BAU exerts its beneficial effect by raising plasma levels of uridine, not by avoiding any supposed toxicity associated with degradation of uridine to uracil. However, as discussed above, Falcone taught that raising levels of uridine in the plasma higher than those achieved by low-dose uridine alone or BAU alone did not result in any improvement in counteracting AZT toxicity.

SEPARATE PATENTABILITY OF CLAIMS 20-21

Claims 20-21 are directed to a method for preventing or treating toxicity due to a pyrimidine nucleoside analog (e.g. prodrugs of arabinosyl cytosine) comprising administering to an animal an acylated derivative of cytidine or deoxycytidine and an inhibitor of cytidine deaminase (e.g. tetrahydrouridine). Claims 20-21 stand rejected under 35 U.S.C. §103 as allegedly being unpatentable over Bhalla et al., Blood 1987 (Bhalla) in view of WO 89/03838 (von Borstel) and U.S. Patent No. 4,017,606 (Hanze). This rejection is based on a mischaracterization of the Hanze reference.

The evaluation of patentability or unpatentability under 35 U.S.C. § 103 is based on factual inquiries, one of which is the content of the prior art. As stated by the Supreme Court in *Graham v. John Deere*:

> "Under § 103, the scope and content of the prior art are to be determined.... Against this background, the obviousness or nonobviousness of the subject matter is determined." *Graham v. John Deere Co.*, 383 U.S. 1, 27, 148 USPQ 459, ___ (1966)

The rejection of claims 20-21 is based on the incorrect assertion that Hanze teaches increasing free cytidine levels with an inhibitor of cytidine deaminase. It is this alleged teaching that is relied on as providing the motivation to combine the cytidine deaminase inhibitor of Hanze with the acylated deoxycytidine of von Borstel. In this regard the rejection stated:

> "Hanze et al. does disclose tetrahydrouridine as a cytidine deaminase inhibitor (column 5, lines 42-6 1) and its use to prevent the degradation of a cytidine nucleoside analog. Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention to have replaced free deoxycytidine with a combination of acylated deoxycytidine and tetrahydrouridine in order to obtain even higher levels of free cytidine in serum and tissue which would create even more reduction in the toxicity of cytidine arabinosie [sic] or any other pyrimidine nucleoside analog." (Paper No. 5, page 6)

As seen from the above-quoted passage, the rejection rises and falls on the premise that Hanze teaches that a cytidine deaminase inhibitor would result in even higher levels of free cytidine in serum and tissue". It does not.

The PTO has not pointed to any explicit teaching of Hanze or other prior art in support of its position that administering an inhibitor of cytidine deaminase would increase levels of free cytidine. Instead, the supposed expectation of increasing *in vivo* cytidine levels by administering a deoxycytidine deaminase inhibitor appears to be based on the more general assumption that inhibiting any given degradative enzyme would be expected to increase the *in vivo* levels of the substrate of that enzyme. While that assumption may be true in some cases, it is not true in others. For example, it was known that inhibiting uridine phosphorylase by administering its inhibitor 5-benzylacyclouridine (BAU) had no effect on plasma uridine in monkeys. This can be seen from the enclosed abstract of Davis, et al., Biochem. Pharmacol. (1993) 45(1): 173-81, which states:

> "In the monkey, BAU (30 mg/kg, i.v.) had no effect on plasma uridine despite the presence of 10-100 microM BAU levels in plasma for 1.5 hr." (Abstract of Davis, et al., "Species-dependent differences in the biochemical effects and metabolism of 5-benzylacyclouridine." (Biochem. Pharmacol. (1993) 45(1): 173-81)

As seen from the above-quoted passage, administering an inhibitor of a degradative enzyme does not necessarily lead to increased plasma levels of the substrate of that enzyme. Therefore, the person of ordinary skill in the art would not have had a reasonable expectation that administering an inhibitor of any given enzyme such as an inhibitor of deoxycytidine deaminase would lead to increased *in vivo* levels of the substrate of that enzyme. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, ____ (Fed. Cir. 1991). A *prima facie* case of unpatentability under 35 U.S.C. **§** 103 has not been made.

SEPARATE PATENTABILITY OF OTHER CLAIM GROUPINGS

With regard to Group 1 (Claims 1-15 and 22-25), arguments for patentability based on non-obviousness are presented in the Appeal Brief filed October 13, 2001, beginning at page 6. With regard to Group 3 (claims 16-17), arguments for patentability based on non-obviousness are presented in the Appeal Brief, beginning at page 10. Those arguments are incorporated herein by reference.

Reversal of the Final Rejection and passage of the subject application to issue are earnestly solicited.

Respectfully submitted,

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